REMARKS

The Office communication mailed 17 October 2006, has been received and its contents carefully reviewed. The Office communication requires Applicants to provide a showing pursuant to 37 CFR 41.202(d) as to why they would prevail against the earliest priority date of U.S. Patent No. 5,985,285, which is 13 March 1996.

Applicants respectfully submit that they reduced to practice prior to 13 March 1996, or in the alternative, conceived of prior to 13 March 1996 and practiced reasonable diligence from before 13 March 1996 to 27 August 1996 the subject matter disclosed in the above-referenced application and the following embodiments (Inventive Subject Matter):

1. An isolated and purified DNA molecule which encodes all of *Yersinia* F1 antigen and all of *Yersinia* V antigen.

2. An isolated and purified DNA molecule which encodes all of *Yersinia* F1 antigen and part of *Yersinia* V antigen.

3. A recombinant DNA construct comprising
(a) an isolated and purified DNA molecule which encodes all of *Yersinia* F1 antigen and all of *Yersinia* V antigen, or
(b) an isolated and purified DNA molecule which encodes all of *Yersinia* F1 antigen and part of *Yersinia* V antigen.

4. A host cell transformed with a recombinant DNA construct comprising
(a) an isolated and purified DNA molecule which encodes all of *Yersinia* F1 antigen and all of *Yersinia* V antigen, or
(b) an isolated and purified DNA molecule which encodes all of *Yersinia* F1 antigen and part of *Yersinia* V antigen.

5. A method of producing a F1-V fusion protein which comprises culturing a host cell transformed with a recombinant DNA construct comprising
(a) an isolated and purified DNA molecule which encodes all of *Yersinia* F1 antigen and all of *Yersinia* V antigen, or
(b) an isolated and purified DNA molecule which encodes all of *Yersinia* F1 antigen and part of *Yersinia* V antigen
and isolating the F1-V fusion protein.

6. An isolated and purified F1-V fusion protein comprising all of *Yersinia* F1 antigen fused to all of *Yersinia* V antigen.

7. An isolated and purified F1-V fusion protein comprising all of *Yersinia* F1 antigen

fused to part of *Yersinia* V antigen.

8. A method of immunizing a subject against plague which comprises administering to the subject an isolated and purified F1-V fusion protein comprising all of *Yersinia* F1 antigen fused to all of *Yersinia* V antigen or an isolated and purified F1-V fusion protein comprising all of *Yersinia* F1 antigen fused to part of *Yersinia* V antigen.

In support, Applicants respectfully submit the following:

1. Affidavit of David G. Heath (Heath Affidavit) and exhibits thereto each having some redacted dates and David G. Heath's curriculum vitae;
2. Affidavit of George W. Anderson, Jr. (Anderson Affidavit) and exhibits thereto each having some redacted dates and George W. Anderson, Jr.'s curriculum vitae;
3. Affidavit of Susan L. Welkos (Welkos Affidavit) and exhibits thereto each having some redacted dates and Susan L. Welkos' curriculum vitae; and
4. Affidavit of Arthur M. Friedlander (Friedlander Affidavit) and exhibits thereto each having some redacted dates and Arthur M. Friedlander's curriculum vitae.

I. ACTUAL REDUCTION TO PRACTICE before 13 March 1996

Applicants respectfully submit that the date of actual reduction to practice of the Inventive Subject Matter was prior to 13 March 1996.

1. Construction of embodiments

Specifically, the Inventive Subject Matter was constructed prior to 13 March 1996. As attested to by Dr. Heath, a DNA molecule encoding all of *Yersinia* F1 antigen fused to all or part of *Yersinia* V antigen was isolated and purified prior to 13 March 1996. See Heath Affidavit, paragraphs 10 and 17, which is supported by Exhibits DH7A, DH7B and DH13 showing gels evidencing the DNA constructs comprising an isolated and purified DNA encoding all of *Yersinia* F1 antigen fused to all or part of *Yersinia* V antigen. Dr. Heath attests that a protein comprising all of *Yersinia* F1 antigen fused to all or part of *Yersinia* V antigen was isolated and purified prior to 13 March 1996. See Heath Affidavit, paragraphs 14 and 18, which is supported by Exhibits DH10 and DH14 showing gels evidencing bands of purified protein consistent with protein comprising all of *Yersinia* F1 antigen fused to all or part of *Yersinia* V antigen. Thus, prior to 13 March 1996, also constructed a host cell transformed with a DNA construct encoding all of *Yersinia* F1 antigen fused to all or part of *Yersinia* V antigen, a method of producing an F1-

V fusion protein comprising all of *Yersinia* F1 antigen fused to all or part of *Yersinia* V antigen.

As attested to Dr. Heath, methods of immunizing a subject with the purified F1-V fusion proteins and immunogenic compositions comprising the purified F1-V fusion proteins were constructed prior to 13 March 1996. See Heath Affidavit, paragraphs 20-23, which is supported by Exhibits 15-18 disclosing mouse challenge assay protocols and vaccine alhydrogel adsorptions comprising an F1-V fusion protein comprising all of *Yersinia* F1 antigen fused to all or part of *Yersinia* V antigen.

Thus, prior to 13 March 1996, Applicants constructed the Inventive Subject Matter – DNA constructs encoding all of *Yersinia* F1 antigen fused to all or part of *Yersinia* V antigen, purified proteins comprising all of *Yersinia* F1 antigen fused to all or part of *Yersinia* V antigen, and immunogenic (vaccine) compositions comprising purified proteins comprising all of *Yersinia* F1 antigen fused to all or part of *Yersinia* V antigen.

2. Determination that the invention would work for its intended purpose

Dr. Anderson obtained alhydrogel preparations having purified F1-V fusion proteins comprising all of *Yersinia* F1 antigen fused to all or part of *Yersinia* V antigen from Dr. Heath and tested the preparations in mouse challenge assays. As attested to by Dr. Anderson, the results of various mouse challenge assays indicated that the purified F1-V fusion proteins would work for its intended purpose of providing protection against infection by *Yersinia pestis*, which is supported by Exhibits GA2 and GA8 and the laboratory notebook page, which was witnessed by Dr. Heath, wherein Dr. Anderson wrote the following:

> Data on page 131 is the first direct evidence that the F1-V fusion protein can induce an immune response to both the F1 and V portions of the F1-V fusion protein. This is the first proof of the concept of making a fusion protein which could be used as an immunogen in a future plague vaccine.

Exhibit GA2 shows the results of mouse challenge assays evidencing that a fusion protein comprising all of *Yersinia* F1 antigen fused to part of *Yersinia* V antigen provides protection against $F1^+$ *Yersinia* strains (CO92), and weak protection against $F1^-$ *Yersinia* strains (C12). Exhibit GA8 shows the results of mouse challenge assays evidencing that a fusion protein comprising all of *Yersinia* F1 antigen fused to all of *Yersinia* V antigen provides protection

against $F1^+$ *Yersinia* strains (CO92) and $F1^-$ *Yersinia* strains (C12).

Therefore, prior to 13 March 1996, Applicants determined that the Inventive Subject Matter – purified proteins comprising all of *Yersinia* F1 antigen fused to all or part of *Yersinia* V antigen and immunogenic (vaccine) compositions comprising purified proteins comprising all of *Yersinia* F1 antigen fused to all or part of *Yersinia* V antigen – would work for its intended purpose.

3. Evidence corroborating inventors' testimony

The inventors' affidavits and experiments and data recorded in their laboratory notebook pages are independently corroborated by the AIBS Peer Review to USAMRMC Medical Biological Defense Research Program on Plague signed by Kathleen McDonough on 12 March 1996. See Exhibit DH19. The AIBS Peer Review Panel consisted of three scientific reviewers having collective knowledge of *Yersinia pestis*, vaccine production, molecular genetics and FDA requirements for a vaccine. The AIBS Peer Review Panel read the abstracts, including Abstract 17, prior to 15 February 1996. The AIBS review notes that "... a construct was made containing the F1 and V antigen genes for expression of a fusion protein. When the F1-V fusion protein was used for immunization, mice were protected when challenged by needle or aerosol with either the F1 positive of F1 negative stain of *Y. pestis*. See Exhibit DH19, pages 15-16.

Additionally, the meeting notes of Dr. Welkos evidences that Dr. Heath made the DNA construct encoding all of the F1 antigen fused to part of the V antigen (Exhibits SW1 and SW5), Dr. Heath purified an F1-V fusion protein which required a good monoclonal antibody against V antigen for further testing (Exhibit SW2), and the mouse challenge studies of Dr. Anderson showed that the fusion protein comprising all of *Yersinia* F1 antigen fused to part of *Yersinia* V antigen provides protection against $F1^+$ *Yersinia* strains (CO92), and weak protection against $F1^-$ *Yersinia* strains (C12) (Exhibit SW4).

Thus, Applicants respectfully submit that the AIBS Peer Review Panel sufficiently corroborates the Applicants reduction to practice of the Inventive Subject Matter.

4. No abandonment, suppression or concealment

Applicants respectfully submit that from the time that they actually reduced the Inventive

Subject Matter to practice to the time of filing the instant application, i.e. 27 August 1996, they did not abandon, suppress or conceal the Inventive Subject Matter. See Affidavit of Dr. Friedlander, paragraph 12. In fact, the Applicants conducted further research and development during the period ranging from after 13 March 1996 to 27 August 1996 which evidences that Applicants had no intention to abandon, suppress or conceal the Inventive Subject Matter.

Therefore, the Applicants did not abandon, suppress or conceal the Inventive Subject Matter from the time of actual reduction to practice to 27 August 1996.

II. CONCEPTION and REASONABLE DILIGENCE

1. Conception

In the alternative, Applicants respectfully submit that they conceived of the Inventive Subject Matter prior to 13 March 1996 and then practiced reasonable diligence from just prior to 13 March 1996 to 27 August 1996.

Specifically, prior to 13 March 1996, Dr. Friedlander conceived of vaccine against plague comprising a fusion protein containing all of F1 antigen fused to all or part of the V antigen. Consequently, prior to 13 March 1996, Dr. Heath volunteered to make the fusion protein and conceived of DNA molecules encoding all of F1 antigen fused to all or part of the V antigen which is evidenced by the primers and PCR plan set forth in his laboratory notebook. See Exhibits DH1, DH4, DH6A and DH12. This is corroborated by the invention disclosure submitted by Dr. Friedlander and the Dr. Welkos' meeting notes. See Exhibits DH3/AF5 and DH6B/SW5. The pictures of the gels in the laboratory notebooks of Dr. Heath evidence that the DNA molecules encoding all of F1 antigen fused to all or part of the V antigen were physically obtained prior to 13 March 1996. See Exhibits DH2, DH7A, DH7B, DH13, and DH17 (sequencing results of clones containing DNA). This is corroborated by Dr. Welkos' meeting notes. See Exhibit DH5/SW1. The Western blots and SDS-PAGE gels in the laboratory notebooks of Dr. Heath evidence that purified fusion proteins comprising all of F1 antigen fused to all or part of the V antigen were physically obtained prior to 13 March 1996. See Exhibits DH9, DH10, DH14, and DH14. Thus, prior to 13 March 1996, Applicants conceived of DNA constructs and purified proteins comprising all of F1 antigen fused to all or part of the V antigen.

Prior to 13 March 1996, Dr. Anderson tested the purified fusion proteins containing all of

F1 antigen fused to all or part of the V antigen in mouse challenge assays to determine their efficacy against infection by *Yersinia pestis*. See e.g. Exhibits GA1-4, GA7, and GA8. The fusion protein containing all of F1 antigen fused to part of the V antigen provided protection against $F1^+$ *Yersinia pestis* (Exhibit GA2) and the fusion protein containing all of F1 antigen fused to all of the V antigen provided protection against $F1^-$ *Yersinia pestis* (Exhibit GA8). Dr. Heath witnessed Dr. Anderson's notebook which provides that the mouse challenge study data obtained prior to 13 March 1996 evidence that the fusion proteins can induce a protective immune response against *Yersinia pestis*. Thus, prior to 13 March 1996, Applicants conceived that a purified fusion protein containing all of F1 antigen fused to part of the V antigen would provide protection against $F1^+$ *Yersinia pestis* and the fusion protein containing all of F1 antigen fused to all of the V antigen would provide protection against $F1^-$ *Yersinia pestis*.

The fact that fusion proteins comprising all of F1 antigen fused to all or part of the V antigen were indeed isolated, purified and tested prior to 15 February 1996, which experimental data was reviewed by an independent review panel further corroborates that Applicants conceived of and reduced to practice or obtained (a) an isolated and purified DNA encoding all of *Yersinia* F1 antigen fused to all or part of *Yersinia* V antigen, (b) a recombinant DNA construct comprising an isolated and purified DNA encoding all of *Yersinia* F1 antigen fused all or part of *Yersinia* V antigen, (c) a host cell transformed with the DNA construct, (d) a method of producing an F1-V fusion protein comprising all of *Yersinia* F1 antigen fused to all or part of *Yersinia* V antigen, (e) the purified F1-V fusion proteins, and (f) methods of immunizing a subject with the purified F1-V fusion proteins. See the AIBS Peer Review to USAMRMC Medical Biological Defense Research Program on Plague signed by Kathleen McDonough on 12 March 1996. See Exhibit DH19.

2. Reasonable Diligence

From at least a date just prior to 13 March 1996 to 27 August 1996, Applicants practiced reasonable diligence in reducing the Inventive Subject Matter to practice and/or filing the above-referenced patent application. Specifically, as attested to Dr. Anderson, up to 27 August 1996, Dr. Anderson conducted further mouse challenge studies which examine the long-term protective efficacy of the protein comprising all of *Yersinia* F1 antigen fused all of *Yersinia* V antigen,

preferred adjuvant concentration ranges, lethal/high dose challenge studies, preferred protein concentrations/amounts and comparison challenge studies comparing other vaccines. See Anderson Affidavit, paragraph 16, which is corroborated by Exhibits GA10-18 and Welkos Affidavit, paragraphs 10-11, and Exhibits SW7 and SW8. Dr. Friedlander compiled the research and data obtained some time before 16 April 1996 and prepared an invention disclosure which was submitted to ORTA of USAMRMC. The invention disclosure was then forwarded to Sana Pratt for preparing and filing a utility patent application with the U.S. Patent & Trademark Office which was diligently filed on 27 August 1996.

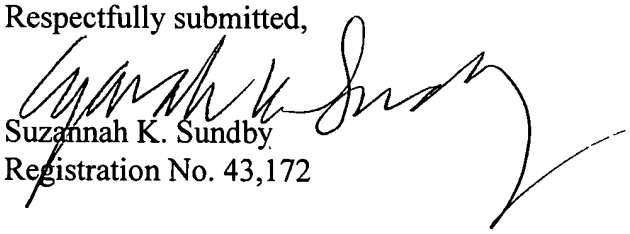
Therefore, Applicants respectfully submit that they practiced reasonable diligence in constructively reducing the Inventive Subject Matter to practice from just prior to 13 March 1996 to the filing date of the instant patent application.

CONCLUSION

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Therefore, it is respectfully requested that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Official action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

It is not believed that extensions of time are required, beyond those that may otherwise be provided for in accompanying documents. However, in the event that additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. 1.136(a), and any fees required therefor are hereby authorized to be charged to **Deposit Account No. 210-380**, Attorney Docket No. **003/029/SAP (RIID 96-08)**.

Respectfully submitted,



Suzannah K. Sundby
Registration No. 43,172

Date: 19 March 2007

SMITH, GAMBRELL & RUSSELL, LLP
1850 M Street, N.W., Suite 800
Washington, D.C. 20036
Telephone: (202) 263-4332
Fax: (202) 263-4352
ssundby@sgrlaw.com